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Original Article

Expression and significance of microRNA-205 in prostate cancer and benign prostatic hyperplasia

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Abstract: Objective: To investigate the significance of microRNA-205 (miRNA-205) expression in prostate cancer. Methods: A total of 88 patients with prostate cancer were included in this study. In addition, 84 patients with prostatic hyperplasia in the same period were selected as controls to observe the relative expression level of miRNA-205 in patients' tissue and evaluate its predictive value in the diagnosis and metastasis of pathologically confirmed prostate cancer. Results: The expression of miRNA-205 in the prostate cancer group was significantly lower than that in the prostatic hyperplasia group, and the differences were statistically significant ($P < 0.001$). The relative expression of miRNA-205 in prostate cancer patients with Gleason score above 7 was lower than that in patients with score below 7 ($P < 0.001$). According to different stages, it's found that the relative expression of miRNA-205 in the T4 group was significantly lower than that in any one of other groups (all $P < 0.01$). The relative expression of miRNA-205 in the N1 stage group with peripheral lymphatic metastasis was lower than that in the N0 stage group without lymphatic metastasis, and the relative expression in the M1 stage group with distant metastasis was lower than that in the M0 stage group without distant metastasis (both $P < 0.01$). The relative expression of miRNA-205 in the high-risk group was significantly lower than that in the low-risk and medial-risk groups, and the differences were statistically significant ($P < 0.001$). ROC curve analysis of prostate cancer and prostatic hyperplasia showed that the area under the diagnostic curve (AUC) of miRNA-205 for prostate cancer was 0.903, the 95% confidence interval was 0.858-0.949, the critical value was 1.724, the sensitivity was 0.929, and the specificity was 0.795. Conclusion: The relative expression of miRNA-205 in the tissue of patients with prostate cancer is down-regulated, which has a high diagnostic value and is related to the malignant degree of the tumor. miRNA-205 may be useful in the diagnosis of prostate cancer and can predict the severity of prostate cancer, which deserves further clinical study.

Keywords: microRNA-205, prostate cancer, diagnosis, predictive value

Introduction

Prostate cancer is one of the most common malignant tumors in men, with the highest incidence in western countries. The latest research found that about 20% of new-onset tumors in the United States are prostate cancer, and its incidence is also gradually increasing in China [1, 2]. Although in recent years there have been great improvements in screening, diagnosis and treatment techniques for prostate cancer, such as screening of prostate-specific antigen density (PSAD) level and robot-assisted radical prostatectomy. However, only androgen deprivation therapy (ADT) can be used for patients who cannot undergo surgery or have contraindications to surgery, and almost all patients are no longer sensitive to this therapy after 1-2 years of treatment and have a poor prognosis [3]. In addition, some studies have found that about 30% of patients have bone metastasis at the time of diagnosing the disease, and almost all patients develop bone metastasis at the late stage [4, 5]. Thus, some studies believe that the degree of bone metastasis can predict the prognosis [6]. Because the expression of prostate-specific antigen (PSA) also increases in patients with prostatic hyperplasia or prostatitis, its early diagnostic specificity is poor [7]. Therefore, positron emission tomography-computed tomography (PET-CT) is often used for early diagnosis of metastatic patients, however, with high cost and huge radiation hazards to patients [8, 9]. Clinically, a biomarker with high

diagnostic specificity and low cost is needed for early screening and determination of metastasis.

At present, there are many studies on biomarkers of prostate cancer, among which miRNA is the most widely studied [10]. MiRNA expression in tumor tissue is closely related to the occurrence and development of the tumor. Studies have found that miRNA-205 plays different roles in different tumors. For example, it has an antineoplastic effect in kidney cancer and breast cancer, but has a promoting effect in non-small cell lung cancer and endometrial cancer [11-14]. One study found that the low expression of miRNA-205 may become an indicator for diagnosis and prognosis of renal cancer [11]. Moreover, a study pointed out that miRNA-205 was highly expressed in both type I and type II endometrial cancer, and played a role in oncogenes possibly through mechanisms such as targeting phosphatase and tensin homolog deleted on chromosome ten, estrogen-related receptors-γ and protein kinase B signal pathways [12]. Hu et al. demonstrated microRNAs expression profiles in 466 invasive ductal carcinomas and 2,399 different types of breast cancers through experiments, speculating that microRNA can be used as a potential molecular biological marker in the diagnosis and prognosis of tumors. Additionally, miRNA-205 was down-regulated in breast cancer patients [13]. In the study of miRNA-205 on lung cancer, it was found that miRNA-205 can inhibit the expression of Smad 4 in non-small cell lung cancer patients, thereby inhibiting cell activity and proliferation, and promoting the growth of lung cancer tumors. Another study showed that miRNA-205 was up-regulated in non-small cell lung cancer tissues, but its expression was not related to the overall survival rate. The expression of miR205 in lung squamous cell carcinoma was higher than that in lung adenocarcinoma, and it could be considered as a specific diagnostic marker for lung squamous cell carcinoma, but its diagnostic accuracy was still uncertain [14]. Previous studies have shown that the down-regulated miRNA-205 expression and targeting PKCε in prostate cancer tissue can regulate the invasion of prostate cancer, promote the progress of prostate cancer, and predict the prognosis of patients [15-17]. In this study, miRNA-205 in prostatic hyperplasia and prostate cancer tissues was determined to explore its expression and clinical significance. At present, PSA is mainly detected in the early screening of prostate diseases with poor specificity. In the study, miRNA-205 was used to detect prostatic hyperplasia and prostate cancer and observe the specificity of them.

Materials and methods

General data

A total of 88 patients with prostate cancer were admitted to our urology department from January 2015 to September 2016 and samples were collected, aged 46-72 years, with an average age of 63.0 ± 8.8 years. Among them, 62 underwent radical prostatectomy and 16 received conservative treatment. Meanwhile, 84 patients with prostatic hyperplasia treated in Qingdao Hiser Hospital were selected as controls, with an average age of 64.4 ± 8.4 years. All the above patients signed the informed consent form, and the study was approved by the Ethics Committee of Qingdao Hiser Hospital.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with prostate cancer and benign prostatic hyperplasia met the criteria established by the Chinese Urological Association of Chinese Medical Association (CUA) 2015 [18, 19]; patients aged 18-75 years; prostate tissues from all patients were obtained by surgical biopsy or electrotomy in our hospital, and stored in a -80°C freezer.

Exclusion criteria: Patients with incomplete clinical data; patients with serious heart, liver, kidney and other diseases; patients with mental illness or cerebrovascular failure; patients with difficult or inconvenient follow-up; patients with other cancers or non-primary prostate cancer.

Methods

Samples (2-3 mm^2) of prostate cancer tissues and prostatic hyperplasia tissues confirmed by pathological sections were taken from the -80°C freezer. The Trizol kit used in this study was purchased from Molecular Research Center Company (U.S.). The extraction of upstream primers and downstream primers was provided by Guangzhou Ruibo Biotechnology Company [20]. RT-PCR was used for reverse transcription miRNA into cDNA using the reverse

transcription kit (Fernentas Company), then DNA was amplified using this template. Finally, the expression of miRNA-205 in prostate tissue samples was determined by fluorescence probe quantitative PCR detection. Specific operation: after the prostate tissue samples were melted and mixed well, 1 mL Trizol was added into 300 μL sample, and kept at room temperature followed by 40 μL DEPC treated water. After extracting total RNA from tissue cells with Trizor for 5 min to its full lysis. Chloroform was added at the ratio of 200 μL chloroform/mL Trizol, and then it was vigorously shaken by hand for 15 s, and kept at room temperature for 15 min. The mixture was centrifuged at 12,000 rpm at 4°C for 15 min. The solution was divided into three layers, the upper water phase dissolving RNA was drawn out and moved to another centrifuge tube. Then 75% ethanol was added at the ratio of 1 mL 75% ethanol/mL Trizol, and the centrifuge tube was gently shaken to suspend the precipitate. The suspension was centrifuged at 7,500 rpm and 4°C for 5 min, then the supernatant was discarded as much as possible. After being dried at room temperature for 5-10 min, the precipitate was dissolved with a kit, the concentration and purity of miRNA-205 were determined with ultraviolet spectrophotometer (Sigma Company of the United States), and miRNA was reverse transcribed into cDNA using the reverse transcription kit (Fernentas Company) with the upstream primer sequence as follows: 5'-TCCTTCATTCCACCG-3' and 5'-GCGAGCACAGAATTAAT-3'. Circulation system (25 μL): SYBR premix (2 ×) 12.5 μL, upstream and downstream primers of the target gene 0.5 μL each, the cDNA template 2.0 μL, and ddH_2O 9.5 μL. Reaction conditions: pre-denaturation at 94°C for 40 min, denaturation at 95°C for 40 s, 60°C for 30 s, 72°C for 30 s, for a total of 35 cycles, and then extension at 72°C for 1 min. Agarose gel electrophoresis was used to detect PCR amplification products. The relative expression was defined by the U6 snRNA expression and analyzed with $2^{-\Delta\Delta C(T)}$. Then, the relative expression of miRNA-205 was determined.

PSA determination

Five mL of fasting venous blood was collected in the morning, sent to the clinical laboratory at 8 o'clock, and analyzed by Beckman automatic biochemical analyzer (Beckman Coulter Co., Ltd., U.S.). The determination was carried out by Abbott i2000 (SR) and chemiluminescence immunoassay kit. Grouping was performed according to PSA > 20 ng/mL and ≤ 20 ng/mL.

Pathological diagnosis of prostate cancer

Gleason grading system was used for clinical grading, and the grading adopted a 5-grade 10-point system [21]. The tumor morphology was divided into 1-5 grades (grade 1 for 1 point, and grade 5 for 5 points); the differentiation degree of tumor was divided into 1-5 grades (grade 1 for 1 point, and grade 5 for 5 points). The sum score of the two is between 2-10 points. The subjects were divided into two groups in this study according to Gleason > 7 points and ≤ 7 points.

TNM staging of prostate cancer

On the basis of 2017 American Joint Committee on Cancer Guidelines for TNM staging of prostate cancer, the clinical staging was determined according to the results of digital rectal examination, chest X-ray, computed tomography, magnetic resonance, bone scan and PET-CT [18]. Clinical tumor stages were divided into T1a, T1b, T1c, T2a, T2b, T2c, T3a, T3b and T4 stages. In this study, T1a, T1b and T1c stages were classified as T1 group, T2a, T2b and T2c stages as T2 group, T3a and T3b stages as T3 group and T4 stage as T4 group. According to the presence or absence of peripheral lymph node metastasis, the subjects were divided into N0 and N1 phases. Also according to whether there was distant metastasis, they were divided into M0 and M1 phases.

Classification of the risk degree of prostate cancer

According to different Gleason score, tumor stage (T stage) and PSA level, the patients were divided into three grades of low, medial and high risk, the risk can be diagnosed by satisfying any of the three parameters, as shown in **Table 1** [22].

Statistical indicators

The SPSS 17.0 statistical software was used to statistically analyze the collected data. The continuous variables were expressed as the mean ± standard deviation ($\bar{x}$ ± sd). Data accorded with normal distribution and homogeneity of variance were compared by t-test

Table 1. Classification of the risk degree of prostate cancer

	Low risk	Medial risk	High risk
Gleason scores	≤ 6	7	≥ 8
PSA (ng/mL)	< 10	10-20	> 20
Tumor stage	≤ T2a	T2b	≥ T2c

Note: PSA, prostate-specific antigen.

Table 2. General data and baseline data of patients with prostate cancer

Item	Case (n, %)
Age	
≥ 65	32 (36.4)
< 65	56 (63.6)
Gleason scores	
> 7	55 (62.5)
7	8 (9.1)
< 7	25 (28.4)
PSA (ng/mL)	
< 10	27 (30.7)
11-20	51 (58.0)
> 20	10 (11.3)
T stage	
T1	19 (21.6)
T2	35 (39.8)
T3	24 (27.3)
T4	10 (11.3)
N stage	
N0	74 (84.1)
N1	14 (15.9)
M stage	
M0	80 (90.9)
M1	8 (9.1)
Classification of the risk degree	
Low risk	16 (18.2)
Medial risk	15 (17.0)
High risk	57 (64.8)

Note: PSA, prostate-specific antigen.

(denoted by t), otherwise by rank sum test (denoted by Z). One-way analysis of variance (ANOVA) was used for detection in multiple groups, and if there were differences, Turkey method was used to make pairwise comparisons. Counting data expressed as cases/percentage (n/%) were analyzed using the Pearson chi-square test and Fisher exact probability (expressed in chi-square). Drawing the ROC curve and calculating the area under the ROC curve (AUROC), including 95% confidence interval (CI), considered that AUROC greater than 0.9 is of high diagnostic ability, and between 0.7 and 0.9 is of moderate efficiency, while between 0.5 and 0.7, the test efficiency is low. The best diagnostic threshold was calculated by the maximum Yoden index method, and the sensitivity and specificity were described. The significance level $P < 0.05$ indicates that the difference is statistically significant.

Table 3. Comparison of relative expression of miRNA-205 between the two groups

Group	miRNA-205
Prostate cancer (n = 88)	0.41 ± 0.29
Prostatic hyperplasia (n = 84)	1.00 ± 0.22
t	-15.025
P	< 0.001

Results

General data and baseline data

This study included 172 patients, 88 with prostate cancer and 84 with benign prostatic hyperplasia, with an average age of 63.0 ± 8.8 years and 64.4 ± 8.4 years, respectively. There was no statistical difference between the two groups in age ($P > 0.05$). See **Table 2**.

Comparison of relative expression of miRNA-205 between the two groups

The relative expression of miRNA-205 was 0.41 ± 0.29 in the 88 patients with prostate cancer and 1.00 ± 0.22 in the 84 patients with prostatic hyperplasia. The expression of miRNA-205 in the prostate cancer group was significantly lower than that in the prostatic hyperplasia group ($P < 0.001$). See **Table 3**.

Comparison of the relative expression of miRNA-205 in the prostate cancer group with different Gleason scores

After the prostate cancer patients were grouped according to different Gleason scores, the levels of miRNA-205 in the two groups were compared. It was found that the relative expression of miRNA-205 in patients with Gleason score above 7 (0.28 ± 0.28) was significantly lower than that in patients with the score below 7 (0.61 ± 0.17), ($P < 0.001$). Correlation analysis showed that $r = -0.704$, $P < 0.001$, and the scores and expression were negatively correlated.

Table 4. Comparison of relative expression of miRNA-205 in different T stage groups

Group	miRNA-205
T1 (n = 19)	0.44 ± 0.29**
T2 (n = 35)	0.47 ± 0.27***
T3 (n = 24)	0.43 ± 0.28**
T4 (n = 10)	0.07 ± 0.05
F	6.055
P	0.001

Note: Compared with T4, **P < 0.01, ***P < 0.001.

Table 5. Comparison of the relative expression of miRNA-205 between different N stages and M stages groups

Group	Case	miRNA-205	t	P
N stage			-2.662	0.009
N0	74	0.44 ± 0.29		
N1	14	0.23 ± 0.22		
M stage			-4.661	0.001
M0	80	0.44 ± 0.28		
M1	8	0.13 ± 0.16		

Comparison of miRNA-205 levels in prostate cancer group with different PSA levels

After the prostate cancer patients were grouped according to different PSA levels, the levels of miRNA-205 were compared between the two groups. The results showed that the relative expression of miRNA-205 in the PSA level > 20 ng/mL group (0.47 ± 0.22) was higher than that in the ≤ 20 ng/mL group (0.49 ± 0.17), but there was no statistical difference between the two groups (P = 0.562).

Comparison of relative expression of miRNA-205 in different T stage groups

According to the comparison of miRNA-205 relative expression in different stages, the relative expression in T4 group was significantly lower than that in other groups (P < 0.01). There was no statistical difference between the other three groups after pairwise comparison (P > 0.05), as shown in **Table 4**.

Comparison of the relative expression of miRNA-205 between different N stages and M stages groups

According to the comparison between different N stages and M stages, the relative expression of miRNA-205 in N1 stage group with peripheral lymphatic metastasis was significantly lower than that in N0 stage group without lymphatic metastasis. The correlation analysis showed that r = -0.280, P = 0.008, and different N stages have negative correlation with expression levels. The relative expression of miRNA-205 in M1 stage group with distant metastasis was significantly lower than that in M0 stage group without distant metastasis (P < 0.05), as shown in **Table 5**.

Table 6. Comparison of relative expression of miRNA-205 with different risk levels

Group	miRNA-205
Low-risk group (n = 16)	0.76 ± 0.18***
Medial group (n = 15)	0.66 ± 0.11***
High group (n = 57)	0.25 ± 0.20
F	63.053
P	< 0.001

Note: Compared with high group, ***P < 0.001.

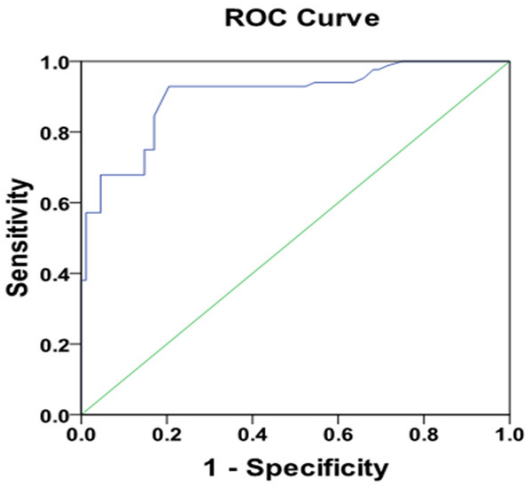

Figure 1. Significance of miRNA-205 in diagnosis of prostate cancer. The blue line is the ROC curve of miRNA-205 in diagnosing prostate cancer, and the green line is the 50% reference line.

Comparison of relative expression of miRNA-205 with different risk levels

According to the comparison of miRNA-205 relative expression in different stages, the relative expression in low-risk and medial-risk groups was significantly higher than that in the high-risk group, with statistical difference (P < 0.001), as shown in **Table 6**.

Significance of miRNA-205 in diagnosis of prostate cancer

In this study, the ROC curve analysis of prostate cancer and prostatic hyperplasia found that the area under the curve (AUC) was 0.903, with a 95% confidence interval of 0.858-0.949, a critical value of 1.724, a sensitivity of 0.929, and a specificity of 0.795, as shown in **Figure 1**.

Discussion

In the study on miRNA, it was found that its inhibition plays a vital role in regulating cell differentiation, proliferation and apoptosis, and is also vital to the occurrence and development of cancer. More than 50% of human malignant tumors are related to miRNA genes [23, 24]. Prostate cancer is one of the most common malignant tumors in men, and its incidence is also on the rise in China [2]. Therefore, for the early diagnosis, recurrence and prognosis of prostate cancer, a biomarker with high diagnostic specificity and low price is needed for early screening and metastasis determination. Research shows that miRNA-205, a key biomarker, is abnormally expressed in malignant tumors such as breast cancer, endometrial cancer, non-small cell lung cancer and prostate cancer [12-14, 25]. Therefore, this study explored the effect of expression level of miRNA-205 on the prediction of the diagnosis and biochemical recurrence of prostate cancer to provide a new diagnostic tool for clinical practice.

In the early diagnosis and screening of prostate cancer, PSA is often used for prediction after measurement. However, because the expression of PSA in patients with prostatic hyperplasia or prostatitis increases, its early diagnosis specificity is poor [7]. This study established three groups of patients with diagnosed prostate cancer, patients with prostatic hyperplasia and healthy patients to compare, and found that miRNA-205 expression in patients with prostate cancer was significantly lower than that in patients with prostatic hyperplasia. Previous studies on miRNA-205 in prostate cancer have found that miRNA-205 works on the resistance of prostate cancer cells by mediating the programmed cell death of B-cell lymphoma/leukemia gene 2L2. The down-regulation of miRNA-205 expression can inhibit chemotherapy-induced programmed cell death levels and further improve the resistance of tumor cells against drugs. The up-regulation of miRNA-205 expression through regulation of target genes can also promote sensitivity to chemotherapeutic drugs, which was consistent with the results of this study [25].

In previous studies on metastasis of prostate cancer in patients, PSA, Gleason score and clinical stage were often used for risk assessment [26]. According to the latest research, patients with prostate cancer who have a PSA of less than 20 μg/mL and a Gleason score of below 7 have a low risk of bone metastasis and do not need a bone scan; otherwise, a bone scan is necessary [21]. Moreover, previous studies have found that prostate cancer is prone to metastasis when Gleason score is between 8 and 10 [27]. Therefore, in this study, the limit of PSA was 20 μg/mL, and the limit of Gleason score was 7. The study found that there was no difference in the relative expression of miRNA-205 between prostate cancer patients with PSA above 20 μg/mL and those with PSA below 20 μg/mL, which might be related to insufficient sample size. However, in this study, the relative expression of miRNA-205 was found to be down-regulated in patients with Gleason score of above 7, which may be related to tumor invasion and proliferation. And the result was in accordance with the above study.

The study on TMN staging of prostate cancer found that, in tumor stage, the relative expression of miRNA-205 in prostate cancer patients at T4 stage was significantly lower than that in other stages. While in N stage, the relative expression at N1 stage with lymph node metastasis was significantly lower than that at N0 stage. In M stage, the relative expression at M1 stage with distant metastasis was significantly lower than that at M0 stage. The increase of tumor volume, the proliferation and differentiation of cancer tissues and the invasion and metastasis of surrounding tissues caused the down-regulation of miRNA-205 expression [11, 12]. According to different Gleason scores, tumor stages and PSA levels, the patients were divided into three groups: low-risk, medial-risk and high-risk groups. It was found that the relative expression of miRNA-205 was relatively high in the low-risk and medial-risk groups and significantly decreased in the high-risk group. As the higher the risk is, the worse the malignancy of the tumor is, and it's indicated that the

worse the malignancy is, the lower the miRNA-205 level is [28]. MiRNA-205 was diagnosed with ROC curve with AUC of 0.903, a sensitivity of 0.929 and a specificity of 0.795, which has a high diagnostic value. We first studied the diagnosed patients to clarify the significance of the indicator, including its significance in diagnosis and differential diagnosis. Then outpatient screening can be conducted for patients in future research. For patients with significant miRNA-205 detection, early relevant examination is of certain importance for early screening of prostate cancer.

Limitations of this study are: the sample size of this study is small and can be further expanded for multi-center research.

To sum up, the relative expression of miRNA-205 in the blood of prostate cancer patients is down-regulated, which has high diagnostic value and is related to the malignant degree of the tumor. Therefore, miRNA-205 may be applied in the diagnosis and prediction of prostate cancer.

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Disclosure of conflict of interest

None.

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